terminal disclaimer is therefore requested.

Rejection Under 35 USC §112, 1¶ and 2¶

Claims 101 and 110 are rejected as allegedly unduly broad and indefinite in view of the number of structures encompassed by the terms "purine," "deazapurine," and "pyrimidine." While it would be apparent to one skilled in the art that Applicants' invention is directed to those purines and pyrimidines which are suitable for incorporation into nucleic acids, the present amendments to Claims 101 and 110 more clearly define this aspect of the invention. The exact nature of the compounds of the invention is exemplified by the specific embodiments and more broadly disclosed in the specification. Based on these teachings, the practitioner would easily be able to identify and make many purines and pyrimidines within the scope of the invention.

The present amendments to Claims 101 and 110 also overcome the rejection thereof based on the term "A represents a component of a detectable complex." The claims now recite "A is a ligand." A ligand is one member of a specifically binding pair of molecules and the term is well understood in the art. See discussion of "A is a ligand," below. Ligands are routinely used in bioassays for their ability to specifically complex with a particular polypeptide (such as an antigen, antibody or receptor) which can then be detected. Many such complexing pairs are well known in the art for labelling and detecting purposes. One skilled in the art would immediately recognize that all of them are suitable for use in the present invention. See British Patent No. 1 564 578, paragraph spanning pages 5-6, and Rosenberg et al. U.S. Patent No. 4,067,774, columns 7-29, copies enclosed. Applicants submit that the recitation "A is a ligand capable of specifically complexing

with a detectable polypeptide" is clear and of a scope commensurate with the instant disclosure.

Applicants maintain that definition of an upper limit on the size of "A" is unnecessary, and that the claims are sufficiently clear, concise and exact to enable one skilled in the art, to whom the language is directed, to make and use the invention claimed. The previously discussed patents, U.S. Patent No. 4,067,774 and British Patent No. 1 564 578, also provide evidence of how one skilled in the art understands the term "ligand." These publications state clearly that the group "ligands" includes such molecules as "...protein, carbohydrate, glycoprotein, steroid, or other organic molecule for which a specific binding partner exists in biological systems or can be synthesized. The ligand, in functional terms, is usually selected from antigens and antibodies thereto; haptens and antibodies thereto; and hormones, vitamins, metabolites and pharmacological agents, and their receptors and binding substances." (British Patent No. 1 564 578, page 5, lines 60-64.) The very same groups of known ligands are taught by Rubenstein et al. in U.S. Patent No. 4,067,774 at columns 7-29. It is therefore clear that a ligand is well understood in the art to mean any of a wide variety of molecules which have the common property of specifically binding another molecule. The cited patents also clearly demonstrate that such ligands can be relatively small (e.g., vitamins or peptides) or very large (e.g., glycoproteins and carbohydrates) and still be useful and substantially interchangeable in inventions, such as the invention presently claimed, which make use of their specific binding properties. It is therefore respectfully submitted that, so as not to include "A" moieties which would be below the minimum level of detection, Applicants teach only a lower limit in the size of "A" as a consideration in selecting an "A" ligand for use in the

invention. As long as the minimum size requirement is met, any other art-recognized ligand (including those known in the art which are very large) can be used as a ligand in the invention. Such diverse ligands, covering a broad range of size, are clearly well known in the art. Placing an upper limitation on the size of "A" should therefore not be required.

The rejection of Claims 101 and 110 for the term "at least one" is mooted by deletion of the phrase by the present amendment.

The last three lines of Claims 101 and 110 have been amended and the previous reference to direct or indirect (e.g., sandwich) detection presented as separate dependent claims for increased clarity. The sandwich and multi-layered sandwich methods of immunological detection are set forth in great detail in the specification and exemplified at pages 34-37. These techniques are not only routine to one skilled in the art of immunological assay, their broad applicability is also well known. Applicants submit that the description of indirect detection is more than sufficient for one of ordinary skill to know the metes and bounds of what is being claimed, given the high level of skill and extensive literature on the subject in this particular art.

In Claims 102 and 111 the term "a moiety which can be detected" has been rendered more clear by recitation of the structural feature of linking the polypeptide to a specific indicator molecule. Examples of such moieties and their linkage to polypeptides so that they can be detected are given at page 2, lines 7-14; page 35, line 28 - page 38, line 16; and page 38, line 18 - page 39, line 9 of the specification. The amended language is submitted to be definite and clear to one skilled in the art.

Applicants respectfully submit that disclosure of a specific embodiment for the claimed cyclic phosphates is not necessary, as it is well known in the art that nucleotides and oligonucleotides containing such cyclic phosphates are functionally similar to nucleotides and oligonucleotides in which the phosphates are not cyclized. It would therefore be routine for one skilled in the art, given the teaching of the specification regarding non-cyclized phosphates and the disclosure of cyclic phosphates, to substitute such cyclic phosphates in the modified nucleotides and oligonucleotides of the invention.

The term "A is a ligand" in Claims 146-148 is submitted to be a term of art which is definite and easily understood by one skilled in the art of such assays. The Rosenberg patent and the British patent discussed above provide extensive teachings of various ligands routinely used in bioassays and the binding substances with which they specifically form complexes. This common property of binding to a specific substance is what makes ligands, as a group, useful in the types of assays Applicants teach. For these reasons ligands are extensively used, well known in the art, and substantially interchangeable in assays of this type.

Claims 146 and 147 have been cancelled by the present amendment as substantially duplicative of Claims 101 and 110, and Claim 148 has been appropriately amended to depend from Claims 101 or 110. The amended recitation in Claims 101 and 110 that "A is a ligand capable of specifically complexing with a detectable polypeptide" further defines and clearly describes the type of "A" ligand which is useful in Applicants' invention as part of the detection system.

Claim 149 has been cancelled, mooting the rejection thereof for alleged indefiniteness and nonenablement.

Claims 150 and 151 have also been cancelled, however, the term "indicator molecule" used in new Claims 152-156 and amended claims 102 and 111 is similar. This term is precisely defined, as such detectable molecules are routinely used and well known in the bioassay art. In new Claim 154 the terms "enzyme" and "detectable product" has been more precisely defined as those enzymes routinely used in bioassays for producing visually-detectable reaction products. Applicants also respectfully submit that one of ordinary skill in this and many related arts understands the meaning of the term "substrate of an enzyme." This term and its definition are found in basic introductory textbooks such as Biochemistry by Lubert Stryer (see page 184 "FORMATION OF AN ENZYME-SUBSTRATE COMPLEX IS THE FIRST STEP IN ENZYMATIC CATALYSIS," copy enclosed):

> "Much of the catalytic power of enzymes comes from the bringing substrates together in favorable orientations in enzyme-substrate (ES) complexes. The substrates are bound to a specific region of the enzyme called the active site. Most enzymes are highly selective in their binding of substrates."

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that this application is in condition for allowance. An action passing this case to issue is therefore respectfully requested.

Respectfully submitted,

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